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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/691,915	**Applicant(s)** GULATI, ANIL	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 January 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-3 and 5-13*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Response to the Amendment

The Amendment filed on 1/23/2006 in response to the previous Final Office Action (12/01/2005) is acknowledged and has been entered.

Claims 1-3, 5-43 are currently pending.

Claims 14-43 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-3 and 5-13 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5 and 13 **remain** rejected under 35 U.S.C. 102(b) as being anticipated by Patterson et al. (IDS, WO 01/00198, 2001).

Patterson et al. (page 2, line 27 to page 3, line 3 and page 6, lines 13-15) discloses a method of treating cancer, i.e. solid tumors, comprising administering to an individual in need thereof a therapeutically effective amount of an endothelin B an inhibitor of an endothelin B-receptor activity. With regards to the endothelin B inhibitor, the WO document teaches (page 8, lines 16-20) that the endothelin inhibitor includes but is not limited to IRL1620. With regards to the cancer, Patterson et al. teaches (page 6, lines 13-28) that cancer includes but is not limited to ovarian, colon, Kaposi's sarcoma, a breast tumor, a melanoma, a prostate tumor, a meningioma and a liver tumor. With regards to the individual, the WO document teaches (page 7, line 4) that the individual is generally a human subject. Patterson et al further teach (page 23, lines 17-19) that the compositions may be

administered in conjunction with other compositions for the treatment, including but not limited to chemotherapeutics. Thus, while Patterson et al. describes IRL1620 as an inhibitor of endothelium activity and not an "endothelium agonist", the claimed method of using IRL1620 for the treatment of a solid tumor appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Moreover, even though the claims are drawn to a mechanism by which IRL1620 interacts with the endothelin B receptor, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

In response to the rejection, Applicants contend that the rejection is improper because the Patterson et al. reference does not constitute prior art under 102 of the patent act because the Patterson et al. reference does not enable the teachings or claims of the present application as amended. Applicants contend that the factors to be considered in the analysis include (1) the quantity of experimentation necessary to reach the claimed invention from the disclosure of the cited reference, (2) the amount of direction or guidance presented in the reference for reaching the claimed invention, (3) the presence or absence of working examples in the cited reference, (4) the nature of the claimed invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. With regards to the quantity of experimentation needed to reach the claimed invention, Applicants assert that the present application teaches and claims a method of treating cancer by increasing the delivery of

chemotherapeutic agents to a tumor by using an endothelin B agonist to selectively increase blood supply to the tumor, whereas Patterson et al. describes treating cancer through the use of endothelin antagonist which decrease blood flow to tumors. Further, Applicants submit that Patterson et al. teach that endothelin B agonists "enhance proliferation and/or delay differentiation" (Patterson et al., page 7, lines 13-15) and should be used as experimental control when testing the beneficial effects of endothelin antagonists (see, for example, page 26, lines 22-29; page 28, lines 17-19). As such, Applicants argue that because the Patterson et al. reference does not include any beneficial uses of endothelin B agonists in the treatment of cancers, a great deal of experimentation remained following the publication of this reference to reach the claimed invention. With regards to the amount of direction or guidance presented in the cited reference for reaching the claimed inventions, Applicants submit that while the Patterson et al. reference does describe using IRL1620 in the treatment of cancer, this reference mischaracterizes IRL1620 as an endothelin antagonist. Thus, Applicants argue that because endothelin antagonists restrict blood flow to tumors, the Patterson et al. reference does not provide any indication that IRL1620 could be used as an endothelin agonist to increase blood flow to a tumor to selectively increase the delivery of chemotherapeutic agents. With regards to the presence or absence of working examples in the cited reference, Applicants contend that there are no working examples in Patterson et al. that disclose the use of endothelin agonist, and more particularly IRL1620, as agents that can be used to increase blood flow to tumors to selectively increase the delivery of chemotherapeutic agents. With regards to the nature of the claimed invention, state of the prior art, relative skill of those in the art and the predictability or unpredictability of the art, Applicants submit that while cancer researchers are, as a group, highly skilled, the art of developing safe and efficacious treatment protocols is exceedingly challenging and unpredictable. Further, Applicants submit that the presently-claimed invention describes a novel mechanism to enhance the effectiveness of chemotherapeutic agents, wherein the effectiveness of these chemotherapeutic agents is enhanced by selectively increasing their delivery to tumors rather than other non-cancerous parts of the body as seen with more conventionally used global or systemic administration protocols. Moreover, Applicants submit that due to the nature of the claimed invention, the state of the prior art, the relative skill of those in the art, and the unpredictability of this art, a reference disclosing a method of treating cancer by restricting blood flow to tumors through using endothelin antagonist should not be read to enable the wholly-

different claimed invention of using endothelin agonists to increase blood supply to a tumor to selectively increase the delivery of chemotherapeutic agents. With regards to the breadth of the claims, Applicants submit that the present claims, as amended, are not described or taught by the Patterson et al. reference. Moreover, the present application provides data showing that IRL1620 provides an effective mechanism to increase blood supply to tumors, thus providing a mechanism to selectively enhance the delivery of chemotherapeutic agents to the tumor.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that Patterson et al. does not enable the teachings or claims of the present application as amended because Patterson et al. does not disclose or suggest a method of treating a solid tumor comprising administering to a mammal in need thereof a therapeutically effective amount of an endothelin B agonist and a therapeutically effective amount of a chemotherapeutic agent, the Examiner acknowledges that Patterson et al. does not explicitly teach a method of treating a solid tumor comprising administering to a mammal in need thereof a therapeutically effective amount of an endothelin B agonist and a therapeutically effective amount of a chemotherapeutic agent (emphasis added). However, the Examiner recognizes that the presently claimed endothelin agonist, Suc-[Glu9,Ala11,15]-Endothelin-1 (8-21), e.g. IRL1620, is **identical** to the endothelin antagonist used by Paterson et al. (see Patterson et al., page 8, lines 16-20) (emphasis added). Moreover, as admitted by Applicants (above), Patterson et al. "describes using IRL1620 in the treatment of cancer". Furthermore, the Examiner recognizes that Patterson et al teach (page 23, lines 17-19) that the compositions may be administered in conjunction with other compositions for the treatment, including but not limited to chemotherapeutics. As such, Patterson et al. teaches the same active steps, i.e. administration of IRL1620 in combination with a chemotherapeutic agent for the treatment of cancer, as presently claimed. Thus, even though the claims are drawn to a mechanism by which IRL1620 increases blood supply to a solid tumor, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Moreover, the instant situation is amenable to the type of analysis set forth in Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999), wherein the Court held that "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for

the prior art's functioning, does not render the old composition patentably new to the discoverer." 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Assuming, *arguendo*, that the instantly claimed invention is patentable over the teachings of Patterson et al. because the therapeutic amount is a specific concentration which allows IRL1620 to selectively increase blood supply to said solid tumor, the instantly amended claims do not appear to recite a specific concentration. Nor do the claims recite that the concentration is selective for increasing blood supply to the solid tumor. Therefore, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure.

Thus, claims 1-3, 5 and 13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Patterson et al. (IDS, WO 01/00198, 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-6 and 13 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Patterson et al. (IDS, WO 01/00198, 2001) in combination with Rowinsky et al. (N. Engl. J. Med. 1995; 332: 1004-1014).

Patterson *et al* teaches, as applied to claims 1-5 and 13 above, a method of treating a solid tumor comprising administering to a human in need thereof a therapeutically effective amount of IRL1620 and a therapeutically effective amount of a chemotherapeutic agent.

Patterson *et al.* does not teach that the chemotherapeutic agent is paclitaxel.

Rowinsky *et al.* discloses (page 1008, 2nd column to page 1011, 2nd column) paclitaxel and its importance as a chemotherapeutic agent in the treatment of a variety of cancer including but not limited to ovarian cancer, breast cancer, and lung cancer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references in order to treat a cancer patient because each of the therapeutics had been individually taught in the prior art to be successful at treating cancer. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, one of ordinary skill in the art would have a reasonable expectation of success that the combination of IRL1620 as taught by Patterson et al and paclitaxel as taught by Rowinsky et al. could be used in a method for treating a solid tumor. Moreover, the rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to the rejection, Applicants contend that while it is true that Patterson et al. discloses the use of IRL1620 as a cancer treatment that can be used in combination with another chemotherapeutic agent (page 8, line 20; page 23, lines 17-19), this disclosure is based solely on the incorrect characterization of IRL1620 as an endothelin antagonist, when in fact, IRL1620 is an endothelin B agonist. Further, Applicants argue that it is not a proper argument to raise against a new method or discovered mechanism of action under 103 (a) because what is "inherent is not necessarily known" and "obviousness cannot be predicated on what is unknown." See for example, In re Rijckaert, 28, USPQ2d 1955, 1955 (Fed. Cir. 1993) citing In re Spormann, 150, USPQ 449, 452 (CCPA 1966) and In re Newell, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). Moreover, Applicants contend that because IRL1620 is now known to be an endothelin agonist, the Patterson et al. reference teaches away from the presently-claimed invention. For example, Applicants argue that reduced blood supply is thought to inhibit tumor growth and/or survival. Thus, Applicants assert that Patterson et al. describes the use of endothelin antagonist to decrease blood supply to a tumor as a treatment for cancer. As stated earlier, Applicants submit that endothelin agonist in Patterson et al. are described as compounds that "enhance proliferation and/or delay differentiation"

(Patterson et al., page 7, lines 13-15) and should be used as experimental control when testing the beneficial effects of endothelin antagonists (see, for example, page 26, lines 22-29; page 28, lines 17-19). Applicants argue that because IRL1620 is now known to be an endothelin agonist, what Patterson et al. now teaches to one of ordinary skill in the art is that IRL 1620 "enhances proliferation and/or delays differentiation" (Patterson et al. page 7, lines 13-15) and that this compound could be used to block the beneficial effects of endothelin antagonist in the treatment of cancer. Thus, Applicants submit that upon reviewing the Patterson et al. reference, one of ordinary skill in the art would conclude that IRL1620 should not be used in the treatment of cancer, and indeed, could stimulate tumor growth and survival. Secondly, Applicants assert that the Patterson et al. reference describes IRL1620 as a stand-alone treatment, whereas the present application describes IRL1620 as an adjuvant to a treatment. Applicants contend that even if the Patterson et al. reference did teach one of ordinary skill in the art the use of IRL 1620 as a cancer treatment in combination with another chemotherapeutic agent, this teaching still would be fundamentally different than that taught and claimed by the present application. For examples, Applicants submit that the Patterson et al. reference describes the use of endothelin antagonists as cancer treatments in and of themselves, and further, states that the endothelin antagonist could be administered "in conjunction with other compositions for treatment." (Patterson et al., page 23, lines 17-18). However, Applicants assert that the Patterson et al. reference does not describe how another composition would interact with the endothelin antagonist treatment it describes. Thus, Applicants contend that the Patterson et al. reference simply describes the use of two independent treatments in combination with the apparent rationale for producing an additive or synergistic effect. Moreover, Applicants argue that in the present application, there is no claim that an endothelin B agonist would, by itself, provide a beneficial effect in the treatment of cancer, but instead used IRL 1620 as an adjuvant to increase the efficacy (and reduce the unwanted side effects) of chemotherapeutic agents by enhancing the delivery of chosen chemotherapeutic agents to the tumor through selective increase of blood flow to the tumor. As such, Applicants argue that because the fundamental difference, as described supra, and the fact that what is not known cannot be obvious, the present rejections under 35 U.S.C. 103 (a) are not proper.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants contention that the Patterson et al. disclosure is based solely on the incorrect characterization of IRL1620 as an endothelin antagonist, when in fact, IRL1620 is an endothelin B agonist, the Examiner acknowledges that there appears to be a difference in terminology. However, the Examiner recognizes that Patterson et al. teaches the same active steps, i.e. administration of IRL1620 in combination with a chemotherapeutic agent for the treatment of cancer, as presently claimed. In response to Applicants contention that inherency it is not a proper argument to raise against a new method or discovered mechanism of action under 103 (a) because what is "inherent is not necessarily known" and "obviousness cannot be predicated on what is unknown." See for example, In re Rijckaert, 28, USPQ2d 1955, 1955 (Fed. Cir. 1993) citing In re Spormann, 150, USPQ 449, 452 (CCPA 1966) and In re Newell, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989), the Examiner acknowledges and agrees with the decision of Rijckaert. However, the Examiner recognizes that inherency arises in both context of anticipation and obviousness (see MPEP 2112) and further, that the fact patterns involved in Rijckaert appear to be different from the instant situation. In Rijckaert, the Court reversed the rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art. In the instant situation, there does not appear to be any optimization of condition because both the presently claimed compound, e.g., IRL 1620 and active steps are the same as the prior arts disclosure. In response to applicant's argument that Patterson et al. reference teaches away from the presently-claimed invention because IRL1620 is now known to be an endothelin agonist, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Assuming, *arguendo,* that Patterson teaches away from the claimed invention, the Examiner recognizes that a prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (emphasis added) In response to Applicants assertion that Patterson describes IRL1620 as a stand-alone-treatment whereas the present applicants describes IRL1620 as an adjuvant to a treatment, the

Examiner acknowledges that Patterson et al. describes the use of IRL1620 as a cancer treatment. However, the Examiner recognizes that, as admitted by Applicants, Patterson et al. states that the endothelin antagonist, e.g. IRL1620 could be administered in conjunction with other compositions for treatment, such as a chemotherapeutic. Thus, while Applicants contend that the instant claims uses IRL1620 as an adjuvant to increase the efficacy (and reduce unwanted side effects) of chemotherapeutic agents by enhancing the delivery of a chosen chemotherapeutic, it is noted that the features upon which applicant relies (i.e., increasing the efficacy and reducing the unwanted side effects of chemotherapeutic agents) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As such, the claims read on a method of treating a solid tumor comprising the active steps of administering to a mammal in need thereof an endothelin B agonist, e.g. IRL1620, and a therapeutically effective amount of a chemotherapeutic agent which Patterson et al. teach.

Thus, claims 1-3, 5-6 and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Patterson et al. (IDS, WO 01/00198, 2001) in combination with Rowinsky et al. (N. Engl. J. Med. 1995; 332: 1004-1014).

Claims 1-3, 5 and 7-13 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Patterson et al. (IDS, WO 01/00198, 2001).

Patterson *et al* teaches, as applied to claims 1-5 and 13 above, a method of treating a solid tumor comprising administering to a human in need thereof a therapeutically effective amount of IRL1620 in conjunction with therapeutically effective amount of a chemotherapeutic agent.

Patterson *et al.* does not teach that the endothelin B agonist and chemotherapeutic agent are administered simultaneously, as a single composition, as a separate composition or sequentially, wherein the chemotherapeutic agent is administered prior to or after the endothelin B agonist.

However, changes in the sequence of which ingredients are added would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The instant situation is amenable to the type of analysis set forth in In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) where the court held that the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. See also In re Gibson, 39 F.2d 975,

5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.). Thus, the claimed variations in Applicants' process with respect to "time" of administration would have been obvious at the time of Applicants' invention, wherein the optimization of time of administration being well within the capabilities of the artisan of ordinary skill at the time of Applicants' invention.

In response to the rejection, Applicants assert that because claims 7-13 depend from claim 1 as amended, which Applicants believe is now in condition for allowance, withdraw the rejection of claims 7-13.

Because claim 1 stands rejected these arguments have been carefully considered, but are not found persuasive.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
3/3/06